REMARKS

Claims 1 through 33 are pending in this application. Claims 1-5 and 7-33 are currently amended. New claims 34-62 are added.

Claims 1-5 and 7-33 are amended in matters of form, to clarify the antecedent basis for certain terms, and to correct certain typographical and spelling errors.

New claims 34-62 are added. These claims are fully supported by the application as filed. Support for the use of the language "to identify a substance useful as a substance that promotes resistance to cell stress" may found throughout the specification (see, for example, page 4, lines 29-30 and page 5, lines 17-18). Support for claim 34 may found, for example, in original claims 1 and 2. Support for claims 35-57 may found, for example, in original claims 3-25, respectively. Support for claims 58 and 59 may be found, for example, in original claim 31 and on page 42, line 25 through page 44, line 10. Support for claim 60 may be found, for example, in original claim 32 and on page 43, lines 10-13. Support for claims 61 and 62 may be found, for example, on page 6, line 23 through page 7, line 4; page 36, line 27 through page 39, line 11; and page 39, lines 13-31.

Thus, none of these amendments introduces new matter. Therefore, entry and consideration of these amendments is respectfully requested.

I. Homology between GADD34 and GADD34L.

On page 2 of the Office Action the Examiner states: "There appears to be at least 99% homology between GADD34 and GADD34L... How they may differ is queried."

Applicants note that the Examiner has provided no support for the statement that GADD34 and GADD34L have at least 99% homology. To the contrary, a comparison of the amino acid sequence of human GADD34, as set forth as UniProt entry O75807 (provided at Tab A), with that of human GADD34L, as set forth in Figure 3 and SEQ ID NO: 2 of the present application,

indicates that the two proteins are less than 20% identical. Please see the sequence alignment provided at Tab B. Thus, while both proteins are regulatory subunits of the eIF2α PP1c phosphatase, they represent entirely distinct proteins with divergent amino acid sequences.

II. Claim rejections under 35 USC § 101 should be withdrawn.

The Examiner has rejected claims 1-33 under 35 USC § 101 as not supported by either a credible asserted utility or a well established utility. In particular, the Examiner contends that the specification does not teach any substance administered and provides no evidence that any substance found by the claimed method would prevent or treat any disease. The Examiner contends that the specification describes a single compound, 22P19, found by the claimed method and further that the specification does not enable this compound for the functions claimed (*i.e.*, usefulness as a preventive or therapeutic agent for a disease involving an oxidative stress).

Applicants respectfully disagree with the Examiner's contention that the specification does not teach any substance administered and provides no evidence that any substance found by the claimed method would prevent or treat any disease. Further, applicants respectfully disagree with the Examiner's contention that the specification describes a single compound, 22P19, found by the claimed method and further that the specification does not enable this compound for the functions claimed (*i.e.*, usefulness as a preventive or therapeutic agent for a disease involving an oxidative stress).

The specification teaches diseases involving an oxidative stress (see, *e.g.*, page 2, lines 6-22; page 7, line 30 through page 8, line 22; and especially page 8, lines 13-22), including neurodegenerative disorders (see, *e.g.*, page 2, lines 19-22 and page 8, lines 18-20). The specification further teaches that diseases involving an oxidative stress may be prevented or treated by activation of the Integrated Stress Response pathway while not causing stress (see, *e.g.*, page 8, lines 23-25; page 3, lines 23-30; and page 4, lines 1-5). The specification further teaches that diseases involving an oxidative stress may be prevented or treated by administering to a patient in need of such treatment an effective amount of a GADD34L inhibitor (see, *e.g.*, page 43, lines 7-13).

In particular, the specification teaches that an effective amount of a GADD34L inhibitor activates the Integrated Stress Response pathway, thereby promoting resistance to cell stress, while not causing stress (*i.e.*, without being toxic) (see, *e.g.*, page 14, lines 17-18; page 43, lines 7-20; page 2, lines 26-28; and page 4, lines 9-17).

The specification provides guidance as to how to identify an effective amount of a GADD34L inhibitor (*i.e.*, an amount of a GADD34L inhibitor that activates the Integrated Stress Response without being toxic) (see, *e.g.*, page 43, lines 16-20 and page 37, line 6 through page 39, line 11). In particular, the specification teaches amounts of the GADD34L-inhibitor 22P19 that activate the Integrated Stress Response without being toxic (see, *e.g.*, page 37, line 28 through page 39, line 11), and amounts of an inhibitory GADD34L siRNA that activate the Integrated Stress Response without being toxic (see, *e.g.*, page 37, lines 6-26).

The specification further teaches that GADD34L inhibitors are protective against oxidative stress. In particular, the specification teaches that glutamate induces oxidative stress (see, *e.g.*, page 42, lines 28-29) and that GADD34L inhibitors protect cells from glutamate toxicity, *i.e.*, from oxidative stress (see, *e.g.*, page 39, lines 13-31; page 6, line 23 through page 7, line 4; and Figure 6).

The specification provides guidance as to how to identify an amount of a GADD34L-inhibitor that protects cells from oxidative stress (see, *e.g.*, page 39, lines 13-31; page 6, line 23 through page 7, line 4; and Figure 6). In particular, the specification teaches amounts of the GADD34L-inhibitor 22P19, and amounts of an inhibitory GADD34L siRNA, that protect cells from glutamate toxicity, *i.e.*, from oxidative stress (see, *e.g.*, page 39, lines 13-31; page 6, line 23 through page 7, line 4; and Figure 6).

The specification further teaches that an effective amount of a GADD34L inhibitor may be administered to prevent or treat disease involving an oxidative stress, for example, by administration to patients undergoing cardio-pulmonary bypass, to head trauma patients or to epileptics (see, *e.g.*, page 43, line 21 through page 44, line 10). At the time of filing, it was within

the skill of one of ordinary skill in the art, *i.e.*, a physician or surgeon, to identify a patient in need of treatment for a disease involving an oxidative stress (*e.g.*, a patient undergoing cardio-pulmonary bypass, a head trauma patient, or an epileptic) and to devise an appropriate treatment regimen, wherein an effective amount of a GADD34L-inhibitor, as identified according to the methods described in the specification, is administered to said patient.

Therefore, applicants respectfully submit that the specification teaches the administration of GADD34L inhibitors to treat or prevent diseases involving an oxidative stress, and teaches that GADD34L inhibitors identified by the claimed method prevent or treat a disease involving an oxidative stress. Further, applicants respectfully submit that the specification describes at least two compounds, 22P19 and a GADD34L siRNA, found by the claimed method, and also discloses both teaching and experimental evidence sufficient to credibly ascribe to these compounds the asserted utility of usefulness as a preventive or therapeutic agent for a disease involving an oxidative stress.

The Patent Office Guidelines for compliance with the utility requirement of 35 USC § 101 call for disclosure of a specific and substantial utility that is credible (see MPEP 2107). The present specification discloses a utility (screening for therapeutic agents) that is both specific (a screen for test substances that inhibit the activity of GADD34L) and substantial (to identify pharmacological agents useful to treat a disease involving an oxidative stress). The asserted utility is credible in that the present specification also discloses two specific pharmacological agents identified as inhibitors of GADD34L (the compound 22P19 and a GADD34L siRNA), which are shown to activate the Integrated Stress Response without being toxic and to protect cells against oxidative stress. These demonstrated biological activities are sufficient to establish that these agents are useful to treat a disease involving a oxidative stress. Applicants note in particular MPEP 2107.01, which states that where an applicant discloses a specific biological activity of a compound and reasonably correlates that activity to a disease condition, such disclosure is sufficient to satisfy the utility requirement.

In conclusion, based upon the disclosure of the present application, the asserted specific and substantial utility would be considered credible by one of ordinary skill in the art. Accordingly, it is respectfully requested that the claim rejections under 35 USC § 101 be withdrawn.

III. Claim rejections under 35 USC § 112, first paragraph, should be withdrawn.

The Examiner has rejected claims 1-33 under 35 USC § 112, first paragraph, for lack of enablement. The Examiner contends that the specification does not enable one of ordinary skill in the art to know which substance would prevent or treat a disease involving an oxidative stress and that the specification contains no description of administering a compound identified by the claimed method.

Applicants respectfully disagree with the Examiner's contention that the specification does not enable one of ordinary skill in the art to know which substance would prevent or treat a disease involving an oxidative stress and contains no description of administering a compound identified by the claimed method.

The specification teaches that any GADD34L inhibitor identified by the method of the invention is a substance useful as a preventive or therapeutic agent for a disease involving an oxidative stress (see, *e.g.*, page 4, lines 9-17). In particular, the specification teaches that an effective amount of a GADD34L inhibitor activates the Integrated Stress Response pathway, thereby promoting resistance to cell stress, while not causing stress (*i.e.*, without being toxic) (see, *e.g.*, page 14, lines 17-18; page 43, lines 7-20; page 2, lines 26-28; and page 4, lines 9-17), and that diseases involving an oxidative stress may be prevented or treated by administering to a patient in need of such treatment an effective amount of a GADD34L inhibitor (see, *e.g.*, page 43, lines 7-13).

The specification teaches a simple assay by which to identify an effective amount of a GADD34L inhibitor (*i.e.*, an amount of a GADD34L inhibitor that activates the Integrated Stress Response without being toxic) (see, *e.g.*, page 43, lines 16-20 and page 37, line 6 through page 39, line 11). In particular, the specification teaches amounts of the GADD34L-inhibitor 22P19 that

activate the Integrated Stress Response without being toxic (see, *e.g.*, page 37, line 28 through page 39, line 11), and amounts of an inhibitory GADD34L siRNA that activate the Integrated Stress Response without being toxic (see, *e.g.*, page 37, lines 6-26).

The specification further provides a simple assay by which to confirm that an amount of a GADD34L inhibitor is protective against oxidative stress. The specification teaches that glutamate induces oxidative stress (see, *e.g.*, page 42, lines 28-29) and that GADD34L inhibitors protect cells from glutamate toxicity, *i.e.*, from oxidative stress (see, *e.g.*, page 39, lines 13-31; page 6, line 23 through page 7, line 4; and Figure 6). In particular, the specification teaches the use of this assay to identify amounts of the GADD34L-inhibitor 22P19, and amounts of an inhibitory GADD34L siRNA, that protect cells from glutamate toxicity, *i.e.*, from oxidative stress (see, *e.g.*, page 39, lines 13-31; page 6, line 23 through page 7, line 4; and Figure 6).

The specification further teaches that an effective amount of a GADD34L inhibitor may be administered to prevent or treat disease involving an oxidative stress, for example, by administration to patients undergoing cardio-pulmonary bypass, to head trauma patients or to epileptics (see, *e.g.*, page 43, line 21 through page 44, line 10). At the time of filing, it was within the skill of one of ordinary skill in the art, *i.e.*, a physician or surgeon, to identify a patient in need of treatment for a disease involving an oxidative stress (*e.g.*, a patient undergoing cardio-pulmonary bypass, a head trauma patient, or an epileptic) and to devise an appropriate treatment regimen, wherein an effective amount of a GADD34L-inhibitor, as identified according to the methods described in the specification, is administered to said patient.

Therefore, applicants respectfully submit that the specification teaches that GADD34L inhibitors identified by the claimed method prevent or treat a disease involving an oxidative stress, thereby enabling one of ordinary skill in the art to know which substance would prevent or treat a disease involving an oxidative stress. Applicants further submit that the specification teaches the administration of GADD34L inhibitors to treat or prevent diseases involving an oxidative stress, and therefore contains written description for administering a compound identified by the claimed method.

Accordingly, it is respectfully requested that the claim rejections under 35 USC § 112, first paragraph, be withdrawn.

IV. Claim rejections under 35 USC § 112, second paragraph, should be withdrawn.

The Examiner has rejected claims 1-33 under 35 USC § 112, second paragraph, as being indefinite. The claims have been amended, as per the Examiner's suggestion, to clarify the antecedent basis for certain terms and to correct typographical and grammatical errors. It is noted that the claims as filed did not contain typographical errors regarding the alpha symbol, therefore appropriate use of the alpha symbol in the currently amended claims does not constitute an amendment.

Applicants respectfully submit that the amendments to the claims obviate each and every basis for rejection of the claims under 35 USC § 112, second paragraph. Accordingly, it is respectfully requested that the claim rejections under 35 USC § 112, second paragraph, be withdrawn.

V. Conclusions

It is respectfully submitted that the amendments and remarks presented here overcome and/or obviate each basis for objection and rejection set forth in the Office Action. The specification and pending claims, as amended, are all believed to be in immediate condition for allowance. Accordingly, the withdrawal of all objections and rejections is respectfully requested. An allowance is earnestly sought.

It is believed that no additional fees are required for these submissions. However, should it be found that a fee is required or a refund owed for this application, the Director is authorized to credit any overpayments and/or charge any additional fees during the pendancy of this application to our Deposit Account No. 04-0100.

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Respectfully submitted,

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